The use of Patient-Reported Outcomes in patients treated with maintenance hemodialysis

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DOI:
10.1053/j.ajkd.2019.01.035

Document Version
Peer reviewed version

Citation for published version (Harvard):
Anderson, N, Calvert, M, Cockwell, P, Dutton, M & Kyte, D 2019, 'The use of Patient-Reported Outcomes in patients treated with maintenance hemodialysis: a perspective', *American Journal of Kidney Diseases*, vol. 74, no. 3, pp. 399-406. https://doi.org/10.1053/j.ajkd.2019.01.035

The use of Patient-Reported Outcomes (PROs) in patients with End Stage Renal Disease requiring treatment with Haemodialysis.

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Abstract

There is increasing interest in the integration of patient-reported outcomes (PROs) into health care research and clinical practice for the benefit of patients with end stage renal disease receiving haemodialysis (HD). In a research setting, PROs can be utilised as a patient-centred primary or secondary outcome in clinical studies. In routine care, PRO data may be used to support service delivery through benchmarking and audit, or to inform and enhance the care of the individual patient by improving patient-clinician communication.

Despite evidence demonstrating the potential benefits of PROs and prioritisation of these outcomes by patients, their use in kidney disease remains limited. Whilst there are significant methodological and operational challenges for the widespread integration of PROs, there is now consensus that this area should be at the forefront of clinical research and implementation science.

Here we discuss the current use of PROs for patients with end-stage renal disease receiving HD treatment and identify a roadmap for increasing the evidence base and introducing PROs into mainstream clinical practice.

Keywords:
Haemodialysis, patient-reported outcomes, PROs patient-reported outcome measures, routine practice, haemodialysis research, End Stage Renal Disease (ESRD), clinical trial

Introduction

Patients with end stage renal disease (ESRD) receiving haemodialysis (HD) often experience extensive physical symptoms (1, 2) , comparable to patients with advanced cancer (3, 4) and report poor health-related quality of life (HRQoL) (3, 5, 6). This impairment profile is associated with increased hospitalisation and mortality rates (7, 8). This population is highly heterogeneous, with varying underlying renal disease and presentation, often highlighting health disparities across different races, ethnicities and socioeconomic status (SES) (9).

The success of HD management has traditionally been evaluated through biochemical dialysis-related targets (10) and mortality and survival rates (11). Similarly, in research settings, mortality is often used as a primary outcome measure, whereas outcomes such as pain, fatigue and dialysis-free time are not routinely captured, despite evidence that such outcomes are prioritised by patients over their own survival (3, 6, 10, 12, 13). One way to capture this information is using patient-reported outcome (PRO) data. Collection of PROs to provide the patient perspective on their health status/symptom burden offers a unique opportunity to identify and address some of the observed health disparities in the ESRD population, with consequent implications for health policy change.

The FDA define a PRO as ‘any report coming from patients about a health condition and its treatment, without interpretation of the patient’s response by a clinician or anyone else’(14). These data can be gathered via validated instruments, commonly paper or electronic (ePRO) questionnaires. PRO tools may be ‘generic’, measuring HRQoL regardless of underlying disease process, or ‘disease-specific’, assessing the impact of a specific disease, such as kidney disease, and its associated symptoms and/or treatment.

This paper will summarise key aspects of PRO use and implementation in HD research and routine care; highlighting recent developments, gaps in the field and future research priorities.

PROs in HD research

High quality aggregated PRO data collected from clinical trials can be used to inform labelling claims, health policy, and may direct individual care by allowing clinicians and patients to select the ‘best treatment’ from the patient’s perspective (15).

Despite this, PRO collection in HD research remains uncommon (16). In a recent review of the Cochrane Database of Systematic Reviews and Clinicaltrials.gov for all studies involving prevalent patients on maintenance dialysis, quality of life was reported in just 9% of trials (17).

Methodological research has highlighted deficiencies in PRO trial design and reporting; including renal trials (18). Where PROMs are collected, there is often a lack of detail and consistency regarding choice of measure; with different PROs being used to assess the same domain. This variability may prevent meaningful synthesis of results, hindering uptake in practice. Too often PROs are chosen and written into trial protocols based on familiarity and availability rather than assessed for relevance and appropriateness to the research question (19).

Optimising the use of PROs in HD research

The first step towards enhancing PRO capture in HD trials is to reach consensus on what domains should be measured (20, 21). This may be achieved through the development of Core Outcome Sets (COS). Led by the Core Outcome Measures in Effectiveness Trials

(COMET) initiative, COS development draws on consensus methodology, incorporating patient and public involvement, to agree on standardized outcomes to be measured and reported for all trials within a clinical specialty (20). This may lead to consistent collection of more meaningful patient-centered outcomes; reducing outcome reporting bias, aiding meta-analysis and facilitating efficient use of precious health care resources (20, 22-26).

The principal work on COS within nephrology is the SONG initiative (Standardized Outcomes in NephroloGy), formed to establish/implement core outcomes across the spectrum of chronic kidney disease, including HD (SONG-HD).(12, 27, 28) This initiative has identified a wide range of recommended outcomes, with patient involvement being a fundamental principle. However, further work is now required to identify robust PRO measures capable of capturing data across the spectrum of SONG-HD outcomes in a way that is non-burdensome for patients. Additionally, these measures should enable data collection across all patients receiving HD, including those with different language requirements, low educational attainment, cognitive impairment, or the critically unwell (27).

PRO instrument selection

Having identified outcomes of interest, it is important to spend time selecting the optimal measurement tool. The COnsensus-based Standards for the selection of health Measure Instruments (COSMIN) group provide guidelines to aid PROM selection based on a tool's measurement properties, e.g. Validity, reliability, responsiveness and interpretability (Box 1) (23, 29). Recent systematic reviews have highlighted the need for comprehensive exploration of PROs used in HD (11, 30-34) and reviews of PROs for fatigue (35) anaemia (36) and vascular access outcomes in maintenance HD trials (37) are currently taking place as part of the SONG-HD Initiative.

Recent research has supported the KDQOL-36 and KDQOL-SF for use within the dialysis population (11, 38), with the longer KDQOL-SF appropriate for research use and the shorter KDQOL-36 of more use in routine clinical settings (Box 2). However, the authors concluded that further validation work is needed for all measures, particularly with English speakers (11). It is important to note that those measures currently recommended for use in HD do not appear to cover all SONG-HD outcomes. Clearly, work is still needed to identify/develop PROs to fill these gaps.

PRO Trial design, implementation and reporting

As with any trial outcome, PROs should be fully integrated into the design and implementation phases according to best-practice guidelines such as the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) PRO extension. (39) This checklist details 16 items recommended for inclusion in a trial protocol where PROs are primary or secondary endpoint (39). Emerging evidence suggests that robust PRO protocol components aid high quality data collection and subsequent dissemination (40, 41).

Unfortunately, however, PRO trial findings have been poorly reported to date, hindering uptake in practice (18, 41). To address this, the CONSORT (Consolidated Standards of Reporting Trials) PRO extension was developed in 2013 (42). Early evidence suggests that PRO reporting may be improved by journal endorsement and author use of CONSORT PRO (43). It is recommended that HD trialists utilise these best practice guidelines when incorporating PROs in their research.

Implementing PROs in routine clinical HD practice

PROs have multiple potential uses (figure 1). In routine clinical settings PROs may aid patient-clinician and multidisciplinary team communication; enhance shared decision-making (44); and support symptom monitoring and management (45), allowing more personalised care. At an aggregate level, PRO data can be used for audit and benchmarking (46): for example, US Medicare & Medicaid Services mandate that HRQoL is assessed annually for patients receiving long-term dialysis (47).

The International Society of Quality of Life Research (ISOQOL) 'User's Guide to Implementing Patient-Reported Outcomes Assessment in Clinical Practice' (21, 48), identifies key pathway components for PROM integration into routine care:

1. Defining the goals for PRO collection

Given the potential multiple uses of PRO collection (figure 1), it is imperative that the goal for collection is clearly defined.

Research suggests clinicians routinely underestimate patient symptoms (2, 49). There is increasing evidence that regular ePRO collection, both within and in-between clinics can be used to flag poor symptom control and deterioration in functional status. In oncology settings, this has led to improvements in HRQoL, enhanced patient-clinician communication, reduced hospitalisation and increased survival (45, 50-52). In Denmark, the generic PRO system AmbuFlex combines data collected remotely, with PRO-based automated decision algorithms and graphical overviews for symptom monitoring and decision making in nine diagnostic groups including CKD (53). There are many validated symptom assessment tools available for use with patients receiving HD (Box 2).

PROs also have the potential to enhance shared-decision making and advance care planning. Findings from the Dialysis Outcomes and Practice Patterns Study (DOPPS) suggest that patient-reported indicators on physical and mental functioning are prognostic markers (54) and that patients with lower PRO scores on the physical and mental components of the KDQOL-36 have higher mortality rates (55).

2. Selecting Patients, Timing and setting of assessment:

Appropriate timing and frequency of PRO assessment in HD is of great importance. A large proportion of patients receiving HD may exhibit cognitive impairment (56). However, there remains some debate about the exact level of impairment during different phases of the dialysis treatment cycle (56-58). A recent consensus meeting involving patient representatives concluded that PROs should preferably not be recorded during dialysis (31), with PRO experts reflecting that responses given during a dialysis session may be sensitive to the current dialysis experience rather than 'usual' HRQoL. However, further qualitative work to elicit and clarify patient and clinician preferences on the timing of PROs completion is required (59).

Consideration needs to be given to the setting where the PRO is completed. Patients may prefer to complete PROs at home or at the dialysis unit. Further research on where best to collect this information is required.

Repeated assessments allow clinicians to track disease progression and inform changes in care (47). Management of patients receiving HD is complicated by multiple comorbidities, polypharmacy and variables associated with the dialysis treatment itself; consequently patients can experience dramatic changes in their health status (60). Moreover, patients usually dialyse at least 3 times per week for a number of hours, thus the additional patient

burden of completing PROs should be considered (61). Frequent collection of scores without associated intervention has been shown to be burdensome to patients, but data on the optimal frequency of collection of HRQoL information from patients with ESRD is lacking (61). PROs need to be sensitive enough to detect patient-important changes and undertaken often enough to allow accurate recall. A Danish feasibility study of PRO capture in routine practice, reported lower response rates from patients with CKD when compared with other patient groups (53); this needs further investigation.

3. Determining which PRO to use in routine care:

Recent systematic reviews have highlighted the current PROs most appropriate for use in HD settings (11, 30, 32, 33), including PROs which pertain to identified core outcomes such as fatigue (35).Based on a review of psychometric properties (38) Peipert & Hays suggested continued use of the KDQOL-36 for US dialysis center internal quality improvement activity. However, they state that the PROM could be modified by inclusion of Patient-Reported Outcomes Measurement Information System (PROMIS) general health items and fine tuning of the kidney disease-targeted scales (47). The National Institutes of Health PROMIS project uses item response theory (IRT) and computer adaptive technology (CAT) to capture global aspects of HRQoL and has been shown to be a potentially valuable tool to assess impact of chronic kidney disease in paediatric populations (62). CAT simplifies PRO completion by selecting questions with patient-specific relevance This process has a high level of reliability, and low burden, as patient responses are used to guide subsequent questions (63)

Further research is required to identify/develop optimum PROs for routine use in HD settings. Cultural appropriateness and cross cultural reliability of such PROs should be assessed, with issues such as spirituality, which have different resonance for different ethnic groups (64) being considered. Key to this process is patient involvement in both item generation and selection (65). While pre-testing of PRO translations for comprehension, cultural relevance and acceptability is common in studies, research such as that conducted by Peipert et al, which examined differential item functioning between black and white patients on the KDQOL-36, is required before measures can be used to make clinical decisions with confidence across subgroups of patients (66).

The International Consortium on Health Outcomes Measures (ICHOM) has recently published a data collection and reference guide for CKD (38). This includes the establishment of standard outcome sets for use in routine practice for patients receiving HD, along with recommended generic PRO measures. However, the generic measures chosen by the ICHOM CKD working group have not yet been formally validated in the HD population.

4. Mode of administration and scoring:

In 2015, as part of the Transforming Participation in Chronic Kidney Disease programme (TP-CKD) (67), a pilot study was undertaken by the UK Renal Registry involving the collection of patient symptom scores. Patients in 14 Renal Units were asked to complete the Integrated Patient Outcome Scale for Renal (IPOS-Renal) (68) and the EuroQol-5 dimensions-5 levels (EQ-5D-5L) (69). Patients receiving HD were included in the sample. Whilst compliance was good, the use of paper questionnaires proved logistically complicated leading to a time lag between completion and feedback. Furthermore, clinical staff reported difficulty using and interpreting the survey results, requiring the organization of on-site workshops to support teams in interpretation and familiarization of the PRO data (1).

UK and Canadian studies have explored the feasibility of using ePROs in kidney disease, accessed by the patient using electronic devices (70-73). ePROs offer an avenue for the collection of remote PRO data in real-time, allowing health care professionals immediate access to important information to guide care (73). Pittman et al. (70) and Schick-Mazaroff & Molzahn (71-73) have explored the feasibility of ePRO collection, whilst demonstrating that it was feasible to collect ePRO data in dialysis environments, they found further research is needed to overcome measurement challenges, including aspects surrounding the responsiveness of the chosen PRO to changes in clinical condition, as well as practical issues such as IT security and cost.

5. Interpretation and Feedback:

The method of PRO data feedback will vary according to the goals of collection; for example, whether aggregate information is required for service improvement, or individual-level data needed to guide care (74). A recent realist synthesis identified a potential tension between these two goals and a need for further research on incorporating PRO data into the EHR, they questioned if the same PRO could be used for multiple purposes.(75) Individualised PROs that are useful for patient assessment may not be reliable as indicators of service quality and vice-versa. For multiplicity of use, all stakeholders should be effectively engaged in future PRO development (74, 76).

Whatever the objective for collection, careful consideration is required to ensure that PRO scores are easily interpretable by all stakeholders. The information should be meaningful and actionable. How the data is visually displayed will impact its use, with studies suggesting that the preferred formats should be as user-friendly as possible (72), highlighting the importance of involving both patients and clinicians in design stages. Pertinent guidance on PRO data feedback is available from ISOQOL and the Patient-Centred Outcomes Research Institute (PCORI) (77), which highlights the importance of training in PRO administration and interpretation as a key methodological consideration.

Increasingly PRO data collection is being undertaken by Renal Registries (1). Breckenridge et al. (31) report a consensus meeting (2015) held to discuss the routine collection of PRO data within European Renal Registries. Whilst agreeing that registries are an ideal way to collect PROs, they identified several challenges around implementation including resourcing, technological and information governance issues as well as maintaining trust in the data. They highlight the need for further research and collaboration to share best practice.

6. Responding to issues raised:

Tong et al. (2017) recognised that efforts to integrate PRO use in patients receiving HD may be hindered by issues associated with the range of co-morbidities and broader HRQoL outcomes experienced by this patient group, who are receiving a technically demanding treatment (78).

Finkelstein & Finkelstein (79) discussed the challenge of capturing individual's experiences of dialysis through twice-yearly paper PRO collection within US dialysis centres for performance monitoring and internal quality improvement (47). They identified issues that included actioning results and noted that clinicians sometimes had difficulty assisting with problems not directly associated with HD. They recommended that while PRO collection should be mandated, given a lack of hard data on optimum methods of implementation, innovative methods should be considered to incorporate PROs into the EHR of individual patients.

7. Evaluating the Impact of PRO intervention on practice:

It is important that the impact of routine PRO collection is assessed to justify their collection and use (80). The financial and time resource costs associated with administration, interpretation and staff training (47), particularly with IT systems (73), need to be offset against the potential impact of the intervention. Finkelstein & Finkelstein argued that collection of PRO data using standardised questionnaires may not capture the unique experience of the individual (60) and it is recognised there are challenges and frustration associated in the uncovering of PROs where little or no effective intervention exists. Further study is required to assess whether PRO collection in such circumstances could have unintended negative consequences, such as promoting false hope or distress.

Future research

Whilst SONG-HD has identified many outcomes that clearly matter to stakeholders (12, 27, 28), they do not map easily to existing measures, so new instruments may be required, which efficiently capture all required domains in a non-burdensome way. Innovative means of PRO data capture are required. Platforms which can collect, collate and feedback PRO data, via the electronic health record /national renal registries, need further investigation and investment. Development of digital systems using item banks and CAT algorithms could be one way of lessening the burden and allow PRO data collected at specific time points to be used for multiple purposes (63).

It is important to capture the perspectives of the nephrology multidisciplinary team on feasibility, cost and patient acceptance of PROMs. Tong et al. have used qualitative methodology to elicit nephrologists' perspectives on defining and applying PROs in HD (78, 81). Clinicians identified the challenges around the heterogeneity of patient priorities and experiences, limitations of current clinical approaches and health-system level barriers, including cost and resource constraints. The authors acknowledged that not all clinicians agree that a patient-centred approach to care is better than a disease-orientated approach (78). Further work is required to ascertain if these findings are capable of broader transferability.

In terms of overall generalisability, lifestyle outcomes that were given a high priority by patients and caregivers in the SONG-HD initiative were derived from international participants receiving both in-center and Home-HD (12, 27). However, there will be nuances in the implementation of PROs with sub groups of patients receiving HD. In the UK, satellite dialysis units may be run by providers independent of the National Health Service, this means local considerations need to be made, such as IT linkage facilities. As recognised by Zbroezek et al., different clinical environments will provide unique and potentially diverse challenges, therefore real-world testing is imperative (82).

Conclusion

Shared decision-making and the provision of patient-centred care is crucial for excellence in HD provision. The use of PROs in both research and routine clinical settings may facilitate this. However, successful implementation of PROs requires careful planning and evaluation, and data collection must fit into current research study designs and work flow patterns. Addressing issues required for effective implementation will require input and collaboration from a range of stakeholders, particularly patients.

Article Information:

Support: Funding support for lead author from Queen Elizabeth Hospital Kidney Patients Association. MC and DK are partially funded by the NIHR Birmingham Biomedical Research Centre and the NIHR Surgical Reconstruction and Microbiology Research Centre at the University Hospitals Birmingham NHS Foundation Trust and the University of Birmingham. DK is supported by the National Institute for Health Research (NIHR) Post-Doctoral Fellowship Scheme, grant number PDF-2016-09-009. The funders did not have a role in writing the report or the decision to submit for publication. The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health.

Conflicts of interest

MC reports receipt of personal fees from Astellas and Takeda and grants from the NIHR, Macmillan Cancer Support, Health Data Research UK and Innovate UK outside the submitted work.

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Box 1: Overview of Measurement Properties (29)

Reliability	**The extent to which the measure is free from random error**
Reproducibility (Test-test Reliabiity)	i.e. Can the measure yield the same results when repeated.
Internal Consistency	The degree of correlation between different items in the measure.
Validity	**The extent to which the measure assesses what it claims to measure**
Criterion Validity	i.e. How does the measure relate to the 'gold standard', if available.
Content (Face) Validity	i.e. Does the measure cover all the important dimensions of the health condition being assessed, does the measure appear to assess what it intends to assess.
Construct Validity	i.e. Does the measure assess the intended outcome of interest, which is not usually directly observable.
Convergent and Discriminant Validity	Subtypes of construct validity: Convergent validity – can two measures of an outcome that should be theoretically related, actually be observed to be related. Discriminant validity – can measures that are theoretically related be observed to be dissimilar.
Responsiveness	**Can the measure detect change in an outcome over time.**
Interpretability	**The degree to which meaning can be assigned to the scores obtained from the outcome measure**

Box 2 – Examples of Renal specific PROs commonly used in HD settings

Measure	Description
Kidney Disease Quality of life-36 KDQOL-36	A36-item HRQOL measure designed for patients undergoing dialysis, derived from the KDQOL-SF. 3 specific dimensions: (i) signs and symptoms (ii) burden of kidney disease (iii) effects of kidney disease and a generic core derived from the SF-12 (physical and mental scales). Overall scores range from 0-100, with higher scores indicating better HRQOL (38)
Kidney Disease Quality of life-SF KDQOL-SF	An 80-item HRQOL measure designed for patients undergoing dialysis which includes the SF-36 as a generic core (physical and mental scales) supplemented with 8 kidney disease-targeted dimensions and 3 additional QOL dimensions. Scores range 0-100 for each dimension with higher scores indicating better HRQOL (83)
Integrated Patient Outcome Scale – Renal IPOS-Renal	IPOS-Renal is a short measure (11 questions), combining the most common symptoms renal patients experience plus additional items from IPOS on concerns beyond symptoms, such as information needs, practical issues, family anxiety (68, 84)
Edmonton Symptom Assessment System- revised Renal (ESASr: Renal)	Modified ESAS to measure symptom burden in patients receiving dialysis. 10 symptom-specific items, 10 visual analogue scales with a superimposed 0-10 scale: anchor words 'No' at 0 and 'Severe' at 10. Total score range 0-100, with higher scores indicating greater symptom distress and burden (85)
Dialysis Symptom Index (DSI)	DSI is a 30-item symptom and prevalence assessment index for patients receiving haemodialysis. Overall scores for symptom burden and total symptom severity are calculated. Score range 0-150, with higher scores indicating greater symptom severity. Symptoms scored on 5-point Likert scale (86)

Figure 1: The multiple uses of PROs (first published in *The BMJ Calvert et al 2019* [87])